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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,406	02/09/2004	David J. Burke	034008-003	6608

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EXAMINER	
KIM, YUNSOO	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,406	BURKE ET AL.	
	Examiner	Art Unit	
	Yunsoo Kim	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *27,28,33-40 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,29-32 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-42 are pending.

2. Applicant' response to restriction filed on 4/3/06 is acknowledged.
Applicant's election with traverse of Group I, claims 1-26, 29-32 and 41 drawn to a stable, aqueous pharmaceutical formulation is acknowledged.

The traversal is based on that Groups I – III are closely related and examining Groups I-III does not impose serious search burden. This is not found persuasive because as stated in the original restriction requirement, the inventions of Groups I-II are related as product and process of using and the inventions of Groups II and III are different methods which require non-coextensive searches. Further, a prior art search also requires a literature search, it is an undue burden for the examiner to search more than one invention. A prior art reads on a method treating a patient with natalizumab is different from a prior art reads on method of preparing a stable antibody composition. The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 27, 28, 33-40 and 42 are withdrawn from the further consideration by examiner 37CFR 1.142(b) as being withdrawn to a non-elected invention

Claims 1-26, 29-32 and 41 drawn to a stable, aqueous pharmaceutical formulation are under consideration in the instant application.

3. Applicants claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.
However, the provisional application 60/445,818 does not appear to provide adequate written support for the "natalizumab" recited in claims 14, 15, 19 and 32. The provisional application 60/445,818 discloses ANTEGREN®.

4. The use of trademarks has been noted in this application (e.g. MILLIPAK 80® on p. 15). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent application, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-12 and17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a stable aqueous pharmaceutical formulation comprising natalizumab, does not reasonably provide enablement for a stable aqueous pharmaceutical formulation comprising any antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir.1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of the skilled in the art to practice the claimed invention.

The specification does not reasonably provide enablement for "pharmaceutical" formulation.
The claimed limitation "pharmaceutical" is intended to use the claimed antibody formulation in pharmaceutical therapy. The specification does not provide any *in vivo* data to show the antibody formulation is suitable in pharmaceutical therapy for any conditions that are mediated by alpha-4 integrin by an antibody recognizes and binds to alpha-4 integrin (see p. 2, lines 23-25 of the instant application).

Engelhardt et al. indicate that more of risk is associated in targeting alpha 4 subunit of integrin than benefits in a long term therapy because of the side effects associated with JC-virus related progressive multifocal leukoecphalopathy (PML, abstract, p. 2271 in particular). Furthermore, Engelhardt et al. teach that the results of animal model of colitis and human model are not
closely correlated (p. 2270 -2271, overlapping paragraph).

Regarding *in vivo* methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP further states that physiological activity can be considered inherently unpredictable.

The pharmaceutical therapy in the absence of *in vivo* clinical data are unpredictable for the following reasons; (1) the protein may be inactivated or degraded before producing an effect (e.g. such proteolytic degradation, immunological inactivation due to an inherently short half life of protein); (2) the protein may not reach the target area because the protein may not be able to cross mucosa or the protein may be adsorbed by fluids, cells, tissues where the protein has no effect; and (3) other functional properties known or unknown make the protein unsuitable for in vivo therapeutic use (e.g. such as adverse side effects prohibitive to the use of such treatment. See p. 1338 footnote 7 of Ex partes Aggarwal, 23 UPPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 1-6, 9-11, 17, 18 and 29-31 are rejected under 35 U.S.C. 102(b) as being anticipated by WO97/45140.

The '140 publication teaches a stable (e.g. reduced aggregates, p. 3, lines 16-21, in particular) antibody formulation having an antibody concentration of >100mg/ml and about 1.7mg/ml (p. 4, lines 9-13, 1.5g antibody to 100g water, example 4, in particular) comprising phosphate buffer, 0.01% of polysorbate 80 (p. 19, example 4, in particular) and NaCl at pH 5.5 (p. 19, example 4, p. 4-6, in particular).

The '140 publication further teaches the antibody formulation is suitable for humanized antibody (e.g. human monoclonal, p. 4-5 overlapping paragraph, in particular). The '140 publication teaches the antibody concentration of " about 1.7mg/ml" in Example 4, p, 19 because 0.15g of antibody to 100g has concentration of 1.5mg/ml and because of " about", the claimed limitation is anticipated.

As the referenced antibody composition and the claimed composition both comprising antibody at concentration of 1.5mg/ml or greater than 100mg/ml in phosphate buffer, 0.01% of polysorbate 80 and NaCl at pH 5.5, the properties of composition being stable at 2-8°C for at least 6 months and being "isotonic" are inherent. Thus, the reference teachings anticipate the claimed invention.

9. Claims 1, 2, 9-11, 17, 18, 25, 26, 29 and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by the U.S. Pat. No. 6, 914,128 B1.

The '128 patent teaches a pharmaceutical composition comprising antibody at 0.1-250 mg/ml concentration in 1-50mM of sodium phosphate and/or histidine at pH 6, 150mM of sodium chloride, and polysorbate (0.005-0.1%) and isotonic agent (col. 72, lines 34-58).

The '128 patent further teaches that the pharmaceutical composition is suitable for intramuscular or subcutaneous administration (col. 72-73 overlapping paragraph) and an article of manufacture comprising

a container (e.g. vial or ampule, col. 72, line 40). In addition, the '128 patent teaches having minor amounts of auxiliary substances including buffers, preservatives, or surfactants enhance the shelf life or effectiveness of the antibody formulation (col. 72, lines 29-34).

As the referenced antibody composition and the claimed composition both comprising antibody at concentration of 0.1-250mg/ml in phosphate buffer (or further comprising histidine), polysorbate 80 and NaCl, the property of composition being stable at 2-8°C for at least 6 months is inherent. Thus, the reference teachings anticipate the claimed invention

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 7, 8 and 12 are rejected under 35. U.S.C. 103(a) as being unpatentable over WO97/45140.

The teachings of the '140 publication have been discussed, supra.

The '140 publication does not teach the particular concentration of immunoglobulin concentrations (about 5 mg/ml, about 20mg/ml and about 50mg/ml as claimed in claims 7, 8 and 12).

The determination of the optimal amount of the immunoglobulin concentrations (about 5 mg/ml, about 20mg/ml and about 50mg/ml as claimed in claims 7, 8 and 12) is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable imports to the claimed invention absent a showing of any unobvious properties. It is not inventive to discover the optimum or workable ranges by routine experimentation where the general conditions of a claim are disclosed in the prior art. *In re Aller*, 220 F2d 454, 456, 105 USPQ 233, 235 (CCPA1955). MPEP 2144.05

12. Claims 1, 3-8, 12, 15, 16, 18, 23, 24, 30 and 31 are rejected under 35. U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,914,128 B1.

The teachings of the reference have been discussed, supra.

The referenced 0.005%-0.1% polysorbate includes the claimed 0.02% polysorbate (claims 3, 4) or 0.001% to about 2% as in claim 30 and the referenced antibody concentration of 0.1-250mg/ml includes the claimed about 1.7mg/ml as in claim 6, about 5 mg/ml as in claim 7, about 20mg/ml as in claim 8 and 50mg/ml as in claim 12 and the ranges between 15mg/ml to about 50mg/ml as in claim 23 and about 0.01mg/ml to about 200mg/ml as in claim 31.

Therefore, the claimed formulation is an obvious variations of the compositions taught by the reference absent of showing any unobvious differences. It is not inventive to discover the optimum or workable ranges by routine experimentation where the general conditions of a claim are disclosed in the prior art. *In re Aller*, 220 F2d 454, 456, 105 USPQ 233, 235 (CCPA1955). MPEP 2144.05.

Therefore, the invention as a whole was prima facie obvious to one of the ordinary skill in the art at the time the invention was made, as evidenced by reference, especially in the absence to the contrary.

13. Claims 1 and 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,914,128 B1 as applied to claim 12 above, and further in view of Gordon et al. (Gastroenterology, 2001, 121:268-274).

The teachings of the '128 patent have been discussed, supra.

The pharmaceutical composition encompassed by the '128 patent includes various antibodies to cytokine, cytokine receptors, cell surface molecules (col. 76, line 25) as well as monoclonal and human antibodies (claims 65-74, col. 76-78)

The '128 patent does not particularly teach using natalizumab antibody.

However, Gordon et al teaches administering natalizumab, human monoclonal antibody binds to alpha subunits of antibody by intravenous infusion in histidine buffer (p. 269, col. 2, under design).

Therefore, it would have been obvious to one of the ordinary skill in the art at the time the invention was made to substitute the antibody in the formulation taught by the '128 patent with the natalizumab antibody as taught by Gordon et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody formulation taught by the '128 patent can be used for enhancing shelf life and effectiveness of antibody formulation. As the formulation stabilizes any antibody, it is expected that the antibody formulation taught by the '128 patent would stabilize the natalizumab taught by Gordon et al. as well.

From the teachings of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1, 15, 16, 18-22 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6, 914,128 B1 in view of Gordon et al. (Gastroenterology, 2001, 121:268-274).

The teachings of the '128 patent have been discussed, supra.

The '128 patent does not particularly teach using natablizumab antibody.

However, Gordon et al teaches administering natalizumab, human monoclonal antibody binds to alpha subunits of antibody by intravenous infusion in histidine buffer (p. 269, col. 2, under design).

Therefore, it would have been obvious to one of the ordinary skill in the art at the time the invention was made to substitute the antibody in the formulation taught by the '128 patent with the natalizumab antibody as taught by Gordon et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody formulation taught by the '128 patent can be used for enhancing shelf life and effectiveness of antibody formulation. As the formulation stabilizes any antibody, it is expected that the antibody formulation taught by the '128 patent would stabilize the natalizumab taught by Gordon et al. as well.

From the teachings of the references, one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yunsoo Kim whose telephone number is 571-272-3176. The examiner can normally be reached on Monday thru Friday 8:30 - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yunsoo Kim

Patent Examiner
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